肠道菌群与胆汁酸代谢的互作关系

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摘　要：肠道菌群与胆汁酸代谢密切相关，肠道细菌通过调节法尼醇受体和G蛋白偶联受体的表达影响胆汁酸的合成；肠道细菌产生的胆酸盐水解酶和类固醇脱氢酶影响胆汁酸去结合、共价修饰和异构化；肠道细菌通过影响肠黏膜胆汁酸转运载体的表达，影响胆汁酸的重吸收。胆汁酸可破坏细胞膜完整性、损伤DNA或诱导蛋白质变性失活等，从而直接抑制肠道细菌；也可通过刺激肠道上皮产生一氧化氮合酶、白细胞介素等因子，间接抑制肠道细菌的生长、增殖；胆汁酸还可作为诱导物，调节致病菌毒力因子的表达。肠道菌群和胆汁酸与畜禽健康密切相关，两者通过精细复杂的互作机制，影响机体的生理机能。本文总结了肠道菌群与胆汁酸代谢的互作关系及其在调节畜禽机体健康和生产性能过程中的作用。

关键词：肠道菌群；胆汁酸；互作；畜禽健康

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肠道细菌的种类超过1 000种，数量是宿主机体细胞总数的10倍以上。数量众多、种类丰富的肠道细菌对维持机体的正常生理机能具有重要意义。肠道细菌能够促进肠道组织发育成熟[1]，参与调节宿主的免疫功能[2]，帮助宿主摄取营养成分[3]，调节肠–脑轴功能[4]，参与机体物质和能量代谢[5]。肠道菌群与胆汁酸代谢密切相关，肠道细菌影响胆汁酸的代谢和重吸收，而胆汁酸也会对肠道菌群的组成和生长增殖造成显著影响，进而影响肠道、肝脏、脑功能[6-7]。本文总结了肠道菌群与胆汁酸的互作关系及其在调节畜禽机体健康和生产性能过程中的作用。

1　肠道细菌对胆汁酸代谢的影响

胆汁酸的合成在肝脏中完成，至少有17种酶参与该过程。胆汁酸的合成包括常规途径和补偿途径[8]。常规途径又称中性途径，是胆汁酸的主要合成方式，75%以上的胆汁酸由该途

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径合成，该途径合成的第一步是胆固醇7α羟基化，该步反应由胆固醇7α−羟化酶（cholesterol 7α-hydroxylase，CYP7A1）催化，是常规途径的限速步骤。补偿途径又称酸性途径，该途径由线粒体内膜上的胆固醇27−羟化酶（cholesterol 27-hydroxylase，CYP27A1）催化胆固醇27生成27−羟化胆固醇开始，27−羟化胆固醇再经氧化胆固醇7α−羟化酶（oxysterol 7α-hydroxylase，CYP7B1）催化，形成7α−羟基化中间体，该中间体再经固醇环修饰、侧链氧化和截短等一系列步骤，形成胆汁酸[8-10]。肠道细菌影响*CYP7A1*、*CYP27A1*等胆汁酸合成相关酶的表达，影响胆汁酸的合成代谢[7]。与无菌鼠相比，接种肠道细菌后，小鼠回肠上皮细胞表面的法尼醇受体(farnesoid X receptor，*FXR*)表达水平上调，FXR进一步诱导成纤维细胞生长因子(fibroblast growth factor，*FGF*)15/19表达，进而抑制CYP7A1、氧化胆固醇8β−羟化酶（oxysterol 8β-hydroxylase，CYP8B1）等酶的活性，从而抑制胆汁酸的合成[11-13]。Sayin等[7]研究发现，小鼠灌服混合抗生素后，肠道细菌数量显著下降，其肠道*FGF*15表达水平也随之下降，肝脏*CYP7A1*表达水平及其活性降低，胆汁酸的合成能力下降。Li等[14]给小鼠饲喂强抗氧化剂（4−羟基−2,2,6,6−四甲基哌啶−N−烃氧），发现该物质导致小鼠肠道嗜酸乳杆菌数量显著下降，引起厚壁菌属和拟杆菌属菌群比例失调，抑制*FXR*表达，胆汁酸的分泌显著上升。G蛋白偶联受体5（G protein-coupled receptor 5，*TGR5*）在人和动物体中广泛表达，是胆汁酸的细胞内受体，肠道细菌能够通过激活*TGR5*的表达，抑制机体胆汁酸的合成[8,15]。Degirolamo等[16]用乳酸菌、双歧杆菌和嗜热链球菌组成的混合益生菌饲喂小鼠，结果发现，该混合益生菌能够显著增加肠道中厚壁菌属和放线菌属的数量，降低拟杆菌属和变形杆菌属的数量，增加粪便中胆汁酸的排出量，降低肠道*FGF*的表达水平，提高CYP7A1和CYP8B1的活性，从而增加肝脏胆汁酸的产量。这些研究提示，肠道细菌的数量和组成均影响胆汁酸的合成。肠道细菌数量增加，刺激*FXR*或*TGR5*的表达上调，抑制胆汁酸的合成；肠道中的厚壁菌属和放线菌属刺激胆汁酸合成，而拟杆菌属和变形杆菌属则抑制胆汁酸合成。

肠道细菌在胆汁酸修饰过程中发挥重要作用。肠道细菌对胆汁酸的修饰主要包括3种方式：去结合作用（水解结合胆汁酸分子中的牛磺酸或甘氨酸）、差向异构作用和脱羟基作用。双歧杆菌、嗜酸乳杆菌和脆弱拟杆菌等能产生胆酸盐水解酶(bile salt hydrolases，BSHs)，这些酶能够降解胆汁酸分子第24位C原子上的N−乙酰胺键，使牛磺酸或甘氨酸脱离[17]。去结合作用发生后，胆汁酸分子中的羟基暴露出来，厚壁菌属、链球菌属和产气芽孢杆菌等产生的

类固醇脱氢酶(hydroxysteroid dehydrogenase，HSDHs)催化羟基发生脱氢氧化反应，成为次级胆汁酸[10,17]。小鼠肠道中的链球菌、拟杆菌和梭菌等能够产生特异性酶，催化α−鼠胆汁酸、β−鼠胆汁酸分子中的第7位C原子发生差向异构反应，转化为ω−鼠胆汁酸[15,18]。

肠道细菌可影响胆汁酸的重吸收。95%以上的胆汁酸在回肠末端重吸收，胆汁酸的重吸收主要由回肠胆汁酸转运载体介导，该转运载体也称顶端钠依赖性胆汁酸转运载体（apical sodium-dependent bile acid transporter，ASBT）；在小肠前段和结肠中，胆汁酸也可以被动扩散的形式重吸收。Out 等[19]试验表明，肠道细菌能够通过刺激肠道上皮细胞中的心肌转录因子 4（*GATA4*）的表达，抑制 *ABST* 的表达，回肠末端胆汁酸的重吸收减少。肠道细菌还可调节结肠黏膜上促血管生成素 4 的表达，影响胆汁酸的重吸收，其详细机制尚不清楚[20]。

2 胆汁酸对肠道菌群的影响

2.1 影响肠道菌群的组成

肠道细菌与胆汁酸相互作用，胆汁酸也会影响肠道菌群组成。胆汁酸促进胆汁酸代谢菌的生长而抑制胆汁酸敏感菌的增殖[6]。胆管阻塞导致胆汁无法进入肠道，就会引起小肠中细菌过度增殖，甚至易位，这提示胆汁酸会影响肠道细菌的数量[21-22]。小鼠口服 1.25~5.00 mmol/kg 体重的胆汁酸，其肠道菌群中厚壁菌属的比例由 54%升高至 94%~98%，而其中拟杆菌和放线菌的比例则显著降低[23-24]。胆汁酸还可通过 FXR 的作用，刺激诱导型一氧化氮合酶、白细胞介素 18 等的表达和分泌，从而抑制肠道细菌的增殖[25-26]。Parséus 等[27]研究发现，胆汁酸受体 *FXR* 基因缺陷型小鼠的肠道厚壁菌属数量显著上升，而拟杆菌属数量显著下降，这是由于 FXR 受体缺陷时胆汁酸的分泌增加导致的，这提示胆汁酸可通过 FXR 信号通路影响肠道菌群组成。

2.2 直接抑制细菌生长增殖

胆汁酸是一种抑菌活性物质，能够抑制细菌生长增殖。胆汁酸能够引起幽门螺杆菌的形态改变，抑制其生长增殖[28]；蛋白质组学研究则表明，人和猪胆汁酸均能够刺激幽门螺杆菌的应激反应，导致其膜通透性改变，干扰其能量代谢，影响其毒力和定植能力[29]。口服胆汁酸显著抑制结肠溃疡模型大鼠肠道病原菌的过度增殖，抑制病原菌易位，降低血清内毒素浓度，延长模型大鼠生存期[30]。Sannasiddappa 等[31]研究了胆汁酸对金黄色葡萄球菌的影响，结果发现，胆汁酸会引起该菌形态改变，显著降低胞内 pH，损伤细胞膜完整性，导致

细胞膜电位消失，引起细菌死亡。

胆汁酸抑制肠道病原菌生长增殖的分子机制尚不明确。胆汁酸作为一种双亲性分子，具有亲脂、亲水活性，能够破坏磷脂双分子层，引起细胞膜破裂，导致细胞死亡[32]。非结合胆汁酸能够自由扩散通过细胞外膜和内膜，进入革兰氏阴性菌细胞内，引起细胞应激反应，或诱导细胞 RNA 形成二级结构，或导致细胞内蛋白质变性失活，从而抑制细菌增殖[33]。D'aldebert 等[34]研究发现，胆汁酸能够诱导肠道上皮细胞外调节蛋白激酶（extracellular protein kinase，ERK）1/2 信号通路激活，进而激活维生素 D 核受体（vitamin D nuclear receptor，VDR）蛋白，刺激抗菌肽 cathelicidin 的表达和分泌，该抗菌肽再发挥抑菌作用。胆汁酸会损伤大肠杆菌、沙门氏菌 DNA，引起核酸点突变、移码突变，甚至染色体重排，从而抑制细菌的生长增殖，诱导细菌死亡[35]。Leverrier 等[36]利用组学技术进行的研究发现，作为一种表面活性分子，胆汁酸能够进入细菌细胞内，导致热应激休克蛋白等分子伴侣变性而失去正常功能，菌体内新合成蛋白质无法正常折叠，从而导致细菌死亡。也有研究指出，胆汁酸能够与菌体内、外的 Fe^{2+}、Ca^{2+}等二价阳离子螯合，影响细菌运动、细胞分裂、基因表达及趋化作用等生理功能，进而抑制细菌增殖[31]。

2.3　作为信号分子调节肠道细菌的生理功能

为抵抗胆汁酸的损伤作用，一些肠道细菌发生适应性进化，能够抵抗胆汁酸；某些致病菌甚至利用胆汁酸作为小分子诱导物，调节毒力或侵染能力相关基因的表达，促进其在肠道中的定位与侵染。III型分泌系统（type-III secretion system，T3SS）是副溶血弧菌的重要毒力因子，该系统中的副溶血弧菌转录调控蛋白（*Vibrio parahaemolyticus* transcriptional regulatory proteins，Vtr）A 和 C 2 个转录因子形成桶状复合物，该复合物被游离胆汁酸识别结合后，激活下游的 VtrB，VtrB 结合到启动子序列上，激活 T3SS 的转录，诱导下游毒力因子的表达，增强该病原菌毒力[37-38]。脱氧胆酸盐可作为小分子诱导物，诱导空肠弯曲杆菌侵染抗原（*Campylobacter* invasion antigens，Cia）启动子，上调 *Cia* 的表达，从而大幅提升该菌对上皮细胞的侵染能力[39]。Kreuder 等[40]进一步研究发现，胆汁酸能够诱导空肠弯曲杆菌毒力及其定植相关因子的表达，还可刺激 7 种非编码 RNA 的表达上调。肠道胆汁酸能够激活艰难梭菌芽孢受体（*Clostridium difficile* germination-specific protease，CspC），CspC 受到刺激后，艰难梭菌芽孢开始萌发，产生具有感染能力的病原菌[41]。致病性大肠杆菌在胆

汁酸刺激下鞭毛蛋白基因表达显著增强，进而诱导黏附蛋白的表达，上调转铁蛋白、噬铁素等铁摄取基因的表达，从而增强大肠杆菌的侵染能力[42]。

3 胆汁酸–肠道细菌互作与畜禽健康

胆汁酸是由动物肝脏合成分泌的生物表面活性剂，肝脏中合成的胆汁酸经共轭修饰后由胆管进入肠道，发挥生理作用。其主要生理作用是乳化脂肪，使其成为微小脂肪粒，增大其与脂肪酶的接触面积，进而促进脂肪的消化吸收[43-44]。在肉鸡饲粮中添加一定水平的胆汁酸，能够提高脂肪消化率，减轻其肝胆负担，保护肝胆功能，促进毒素的排出[45-46]。此外，胆汁酸还可作为信号小分子，调节动物血液胆固醇、葡萄糖和甘油三酯浓度[43,47]。

胆汁酸代谢障碍会引起动物发生多种疾病。胆酸等初级胆汁酸是艰难梭菌生长必需的营养成分，能够促进该病原菌的增殖，而鹅去氧胆酸、石胆酸等次级胆汁酸则能够抑制艰难梭菌的增殖，防止艰难梭菌感染；当肠道胆汁酸代谢紊乱，其中初级胆汁酸不能正常转化为次级胆汁酸时，就可能发生艰难梭菌感染，引起严重的肠道炎症[48-49]。回肠是胆汁酸重吸收的主要场所，高浓度的胆汁酸刺激回肠 *FXR* 的过度表达，而 FXR 可介导肠道炎症反应，引起回肠功能紊乱[50-51]。此外，肠道胆汁酸水平还与动物胆固醇、脂肪和葡萄糖代谢密切相关，肠道胆汁酸浓度过高或过低，均会引起动物脂肪和糖代谢紊乱，影响其健康和生产性能[52-53]。胆汁酸能够刺激仔猪回肠内分泌细胞中胰高血糖素样肽（glucagon-like peptide，*GLP*）的表达和分泌，而 GLP 可作用于猪胰岛α、β细胞，刺激胰岛素分泌，调节血液葡萄糖浓度[43,54]。肠道胆汁酸水平过高或过低，均会引起猪葡萄糖代谢紊乱，影响机体健康。

肠道菌群与胆汁酸的互作会影响畜禽健康及其生产性能。肠道细菌能够产生 BSHs，调控肠道胆汁酸代谢，影响胆汁酸的组成，而肠道胆汁酸的组成和数量会影响动物的胆固醇和脂肪代谢，进而影响动物的生产性能[55]。拟杆菌属、厚壁菌属和放线菌属等肠道菌能产生 BSHs，该酶能催化肠道胆汁酸的水解和转化，使胆汁酸对脂肪的乳化能力下降，从而抑制机体对脂肪的利用[47]。嗜酸乳杆菌能够产生广谱 BSHs，水解肠道中各种胆汁酸，从而降低肠道胆汁酸浓度，一定程度上抑制动物对脂肪的利用，这可能是益生菌能够改善动物肠道健康，但并未表现出抗生素那样的促生长效果的重要原因[55]。Guban 等[56]对肉仔鸡的研究也发现，饲粮添加杆菌肽锌导致肉鸡肠道中唾液乳杆菌的数量显著下降，细菌来源的 BSHs 的活性随之降低，机体对脂肪的利用率上升，增重速度提高。这提示肠道细菌通过产生 BSHs，

影响肠道胆汁酸浓度，进而影响脂肪的消化吸收。

4 小 结

胆汁酸、肠道菌群和畜禽机体三者间关系密切。研究发现，肠道菌群通过产生 BSHs 等系列酶，对肠道中的胆汁酸进行代谢，进而影响胆汁酸对动物的生理功能；而胆汁酸则会通过系列机制，影响肠道细菌数量和菌群组成，进而影响肠道菌群的生理功能。有关胆汁酸与肠道菌群互作的精确机制，以及这些互作机制对动物健康和生产性能的影响，仍需系统深入的研究。探明肠道菌群与胆汁酸的互作机制，揭示两者互作对机体健康和畜禽生产性能的影响，具有十分重要的理论和实践意义。

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Interacting Relationship between Intestinal Microflora and Bile Acid Metabolism

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Abstract: Intestinal microflora is closely related to bile acid metabolism. Intestinal microflora affect the synthesis of bile acid by regulating expression of farnesoid X receptor and G

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protein-coupled receptor. The bacteria influence the deconjugation, covalent modification and epimervation of bile acid by producing bile salt hydrolases and hydroxysteroid dehydrogenase. The expression of intestinal mucosal bile acid transporters and the reabsorption of bile acid are also regulated by intestinal microflora. Bile acid can directly inhibit the intestional bacteria by destroying the integrity of the bacterial membrane, damaging the DNA, denaturing the protein. Bile acid also can indirectly suppress the growth and proliferation of intestinal bacteria by stimulating intestinal epithelium to producing inducible nitric oxide synthase and interleukin. Bile acid act as an inducer to modulate expression of virulence factors of pathogenic bacteria. The intestinal micoflora and bile acid are closely related to the animal health, which affect animal physiological functions by sophisticated mechanism. This paper reviewed the interacting relationship between intestinal microflora and bile acid metabolism, and the roles of the interaction in regulation of animal health and performance.

Key words: intestinal microflora; bille acid; interaction; animal health